HER3 has become a target for antibody therapy. Various antibodies directed against HER3 have been developed (Gaborit et al. 2015, Hum. Vaccin. Immunother. 12: 576-592; Dey et al. 2015, Am. J. Transl. Res. 7: 733-750; Aurisicchio et al. 2012, Oncotarget 3, 744-758; Baselga & Swain 2009, Nat. Rev. Cancer 9: 463-475; Gala & Chandariapaty 2014, Clin. Cancer Res. 20: 1410-1416; Kol et al. 2014, Pharmacol. Ther. 143: 1-11; Zhang et al. 2016, Acta Biochim. Biophys. Sin. 48: 39-48).

[0012] The complex mechanisms regulating the function of HER3 warrant further research on new and optimized therapeutic strategies against this protein. Accordingly, there remains a need for developing novel, effective and safe products that modulate the activity of HER3 and thus treat HER3-related diseases, such as cancer.

SUMMARY OF THE INVENTION

[0013] The invention is based on the discovery of antibodies or fragments thereof that bind to extracellular region (ectodomain) of HER3 receptor and block both ligand-dependent (e.g. neuregulin) and ligand-independent HER3 signaling pathways. The invention is also based on the discovery of antibodies or fragments thereof that bind to amino acid residues within ectodomain of HER3 and block both ligand-dependent (e.g. neuregulin) and ligand-independent HER3 signaling pathways.

[0014] In another aspect, the invention pertains to isolated antibody or fragment thereof that recognizes an epitope of a HER3 receptor, wherein the epitope comprises amino acid residues within ectodomain of the HER3 receptor, and wherein the antibody or fragment thereof blocks both ligand-dependent and ligand-independent signal transduction.

[0015] In another aspect, the invention pertains to an isolated antibody or fragment thereof to a HER3 receptor, having a dissociation (K_D) of at least 1×10^{-7} M, 10^{-8} M, 10^{-9} M, 10^{-10} M, 10^{-11} M, 10^{-12} M, 10^{-13} M, wherein the antibody or fragment thereof blocks both ligand-dependent and ligand-independent signal transduction.

[0016] In another aspect, the invention pertains to a fragment of an antibody that binds to HER3 selected from the group consisting of; Fab, $F(ab_2)'$, $F(ab)_2'$, scFv, VHH, VH, VL, dAbs, wherein the fragment of the antibody blocks both ligand-dependent and ligand-independent signal transduction.

[0017] The antigen-binding protein that binds to HER3 can be an antibody. The antibody can be a monoclonal antibody, a polyclonal antibody, a recombinant antibody, a humanized antibody, a human antibody, a chimeric antibody, a multi-specific antibody, or an antibody fragment thereof (e.g., a Fab fragment, a Fab' fragment, a F(ab')2 fragment, a Fv fragment, a diabody, or a single chain antibody molecule). The antibody can be of the IgGI-, IgG2-, IgG3- or IgG4-type.

[0018] In another aspect, the invention pertains to a pharmaceutical composition comprising an antibody or fragment thereof and a pharmaceutically acceptable carrier. In one embodiment, the pharmaceutical composition further comprises an additional therapeutic agent. In one embodiment, the additional therapeutic agent is selected from the group consisting of an EGFR inhibitor, a HER2 inhibitor, a HER3 inhibitor, a HER4 inhibitor, an mTOR inhibitor and a PI3 Kinase inhibitor. In one embodiment, the additional therapeutic agent is a EGFR inhibitor selected from the group consisting of Matuzumab (EMD72000), Erbitux®/Cetuximab, Vectibix®/Panitumumab, mAb 806, Nimotuzumab, Iressa®/Gefitinib, CI-1033 (PD183805), Lapatinib (GW-572016), Tykerb®/Lapatinib Ditosylate, Tarceva®/Erlotinib HCL (OSI-774), PKI-166, and Tovok®; a HER2 inhibitor selected from the group consisting of Pertuzumab, Trastuzumab, MM-111, neratinib, lapatinib or lapatinib ditosylate/Tykerb®; a HER3 inhibitor selected from the group consisting of, MM-121, MM-111, IB4C3, 2DID12 (U3 Pharma AG), AMG888 (Amgen), AV-203 (Aveo), MEHD7945A (Genentech), MOR10703 (Novartis) and small molecules that inhibit HER3; and a HER4 inhibitor. In one embodiment, the additional therapeutic agent is a HER3 inhibitor, wherein the HER3 inhibitor is MORI 0703. In one embodiment, the additional therapeutic agent is an mTOR inhibitor selected from the group consisting of Temsirolimus/Torisel®, ridaforolimus/Deforolimus, AP23573, MK8669, everolimus/Affinitor®. In one embodiment, the additional therapeutic agent is a PI3 Kinase inhibitor selected from the group consisting of GDC 0941, BEZ235, BKM120 and BYL719.

[0019] In one aspect, the invention pertains to a method of treating a cancer comprising selecting a subject having an HER3 expressing cancer, administering to the subject an effective amount of a composition comprising an antibody or fragment thereof disclosed herein. In one embodiment, the subject is a human and the cancer is selected from the group consisting of breast cancer, colorectal cancer, lung cancer, pancreatic ductal adenocarcinoma, multiple myeloma, ovarian cancer, liver cancer, gastric cancer, acute myeloid leukemia, chronic myeloid leukemia, osteosarcoma, squamous cell carcinoma, peripheral nerve sheath tumors, schwannoma, head and neck cancer, bladder cancer, esophageal cancer, Barretts esophageal cancer, glioblastoma, clear cell sarcoma of soft tissue, malignant mesothelioma, neurofibromatosis, renal cancer, and melanoma, prostate cancer, benign prostatic hyperplasia, gynacomastica, and endometriosis.

[0020] In one aspect, the invention pertains to a method of treating a cancer comprising selecting a subject having NRG1-rearranged fusions expressing cancer, administering to the subject an effective amount of a composition comprising an antibody or fragment thereof disclosed herein. In one embodiment, the subject is a human and the cancer is selected from the group consisting of breast cancer, colorectal cancer, lung cancer, pancreatic ductal adenocarcinoma, multiple myeloma, ovarian cancer, liver cancer, gastric cancer, acute myeloid leukemia, chronic myeloid leukemia, osteosarcoma, squamous cell carcinoma, peripheral nerve sheath tumors, schwannoma, head and neck cancer, bladder cancer, esophageal cancer, Barretts esophageal cancer, glioblastoma, clear cell sarcoma of soft tissue, malignant mesothelioma, neurofibromatosis, renal cancer, and melanoma, prostate cancer, benign prostatic hyperplasia, gynacomastica, and endometriosis.

[0021] In one aspect, the invention pertains to use of the antibody or fragment thereof for treating subjects having an HER3 associated disease, by administering an agent that binds to HER3, in combination with a second agent that binds to and/or inhibits another member of the HER family. The first and the second agent may be any kind of molecule that binds to HER3 or binds to and/or inhibits another HER family member, respectively, including, but not limited to a biological compound, such as an antigen binding protein, a